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09/302,816	03/03/1998	DEAN L. ENGELHARDT	ENZ-52(C)	7467

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1634	82

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/302,816	Engelhardt et al.
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 13, 2002*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *91-141 and 150-168* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *150-167* is/are allowed.

6) ☒ Claim(s) *91-141 and 168* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 18
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Specification

1. Claim 91 has been amended. Claims 142-149 have been cancelled without prejudice towards further prosecution. New claims 151-168 have been added.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 91-120 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 91-120 are rejected over the recitation of the negative limitations "independent of a requirement for the introduction of an endonuclease." in claim 91, line 4. (See MPEP 2173.05 (I)) -- "Any negative limitation or exclusionary proviso must have basis in the original disclosure. See *Ex parte Grasselli,* USPQ 393 (Bd. App. 1983), *aff'd mem.,* 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C.

112, first paragraph as failing to comply with the written description requirement". In the instant application, the applicant did not identify any basis for the negative limitations "independent of a requirement for the introduction of an endonuclease". Therefore, the amended claims do not have any basis in the original specification.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 168 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 168 recites the limitation "said polymerase" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

7. Claims 91-96 and 99-120 are rejected under 35 U.S.C. 102 (e) as anticipated by Walker et al (U.S. Patent 5,455,166) (October 3, 1995)

This rejection is based on the fact that the mere absence of a positive recitation in the amended claim 91 is not basis for an exclusion. Walker et al teaches an in vitro process for producing more than one copy of a specific nucleic acid, the process being independent of a requirement for the introduction of an intermediate structure for the production of the specific nucleic acid, (Abstract, Figures 1 and 2), the process comprising the steps of:

(a) providing a nucleic acid sample containing or suspected of containing the sequence of the specific nucleic acid (Example 1, column 10, lines 58-63 and Example 2, column 11, line 63 and Example 3, column 12, lines 49-53);

(b) contacting the sample with a mixture comprising:

(I) nucleic acid precursors (Figure 1)

(ii) one or more specific nucleic acid primers each of which is complementary to a distinct sequence of the specific nucleic acid (Figure 1 and Example 2, column 11, lines 56-58), and

(iii) an effective amount of a nucleic acid producing catalyst (Example 1, column 11, lines 1-7); and

c) allowing the mixture to react under isostatic conditions of temperature, buffer and ionic strength, thereby producing more than one copy of the specific nucleic acid (Figures 1 and 2 and Example 2, column 12, lines 3-6).

Walker teaches the process wherein the nucleic acid is single stranded or double-stranded DNA (Figures 1 and 2 and Examples 1 and 2).

Walker teaches the process wherein the nucleic acid is in solution (Example 2, column 11, line 6 56-62).

Walker teaches the process further comprising the steps of treating the specific nucleic acid with a restriction enzyme capable of producing blunt ends (Figures 1 and 2, column 8, lines 20-60 and example 1, column 11, line 5 and example 2, column 12, line 5).

Walker teaches the process wherein the nucleic acid is isolated or purified prior to the contacting step or the reacting step (Example 3, column 12, lines 49-52).

Walker teaches the process wherein the releasing step is carried out by means of a restriction enzyme (Figures 1 and 2).

Walker teaches the process wherein the nucleic acid precursors are selected from nucleoside triphosphate and nucleoside triphosphate analogs, or a combination thereof (column 8, lines 20-60 and Example 3, column 12, line 58).

Walker teaches the process wherein the nucleic acid precursors are selected from ATP, GTP, CTP, UTP or TTP (Figures 1 and 2 and Example 2, column 12, lines 1-3).

Walker teaches the process wherein the nucleoside triphosphate analogs are naturally occurring or synthetic, or a combination thereof (Figures 1 and 2 and Example 2, column 12, lines 1-3).

Walker teaches the process wherein at least one of the nucleoside triphosphate analogs is modified on the phosphate (column 8, lines 20-60 and Example 3, column 12, line 58).

Walker teaches the process wherein the specific nucleic acid primers contains a 3'-hydroxyl group or an isosteric configuration of heteroatoms containing sulfur (Figures 1 and 2 and Example 2, column 11, lines 56-57).

Walker teaches the process wherein the specific nucleic acid primers are not substantially complementary to one another and does not contain more than five complementary to base-pairs in the sequences therein (Column 15, SEQ ID Nos; 5 and 6).

Walker teaches the process wherein the specific nucleic acid primers comprise from about 5 to 100 nucleotides (SEQ ID Nos: 4-7).

Walker teaches the process wherein the specific nucleic acid primers comprise from about 1 to 200 non complementary nucleotides (Column 15, SEQ ID Nos: 5 and 6).

Walker teaches the process wherein the nucleic acid producing catalyst is selected from DNA polymerase (Example 1, column 11, lines 1-5).

Walker teaches the process further comprising the step of detecting the product by means of incorporating into the product a labeled primer (Example 3, column 12, line 65 to column 13, line 13 and Table III).

Walker teaches the process further comprising the step of regenerating the one or more specific nucleic acid primers for additional production processes (Figures 1 and 2).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 97-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker (U.S. Patent 5,455,166) (October 3, 1995) in view of Matthews et al. (Analytical Biochemistry, (1988), Vol. 169, pages 1-25).

Walker teaches the processes of claims 91-96 and 99-120 as described above.

Walker does not teach the isolation or purification of the specific nucleic acid by means of sandwich hybridization or capture sandwich hybridization.

Matthews et al teaches the isolation or purification of the specific nucleic acid by means of sandwich hybridization or capture sandwich hybridization (Figures 9, 10, 12, 13 and 14).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute sandwich hybridization model of Matthews et al. in the method of Walker, since Matthews et al states, "The sandwich hybridization strategy is not limited

to quantitation of a nucleic acid species, but can easily be applied to detection of altered restriction sites in DNA, providing the exact mutation to be detected is known (page 16, column 1, lines 7-11)."An ordinary practitioner would have been motivated to combine the sandwich hybridization model of Matthews et al. in the method of Walker, in order to achieve the express advantages noted by Matthews et al. of a method which provides easy application to detection of altered restriction sites in DNA.

10. Claims 121-136 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker (U.S. Patent 5,455,166) (October 3, 1995) in view of Pardee et al. (U.S. Patent 5,965,409) (October 12, 1999).

Walker teaches the processes of claims 91-96 and 99-120 as described above.

Walker does not teach primers comprising at least one ribonucleic acid segment.

Pardee et al teaches primers comprising at least one ribonucleic acid segment (Column 1, line 66 to Column 2, line 7).

Walker does not teach removing of primer-coded sequences from the product by digestion with an enzyme ribonuclease H.

Pardee et al teaches removing of primer-coded sequences from the product by digestion with an enzyme ribonuclease H (Column 1, line 66 to Column 2, line 7).

Walker does not teach one or more specific chemically-modified primers each of which primer is substantially complementary to a distinct sequence of the specific nucleic acid.

Pardee et al. teaches one or more specific chemically-modified primers each of which primer is substantially complementary to a distinct sequence of the specific nucleic acid (Column 1, line 66 to Column 2, line 7).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the chemically-modified primers made by RNAse H of Pardee et al. in the method of Walker, since Pardee et al state, "This reaction is very efficient (Column 2, lines 5-6)." By employing scientific reasoning, an ordinary practitioner would have been motivated to substitute and combine the chemically-modified primers made by RNAse H of Pardee et al. in the method of Walker, in order to produce more than a copy of a specific nucleic acid and also in order to achieve the express advantages , as noted by Pardee et al., of a reaction which is very efficient.

11. Claims 137-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker (U.S. Patent 5,455,166) (October 3, 1995) in view of Pardee et al. (U.S. Patent 5,965,409) (October 12, 1999) further in view of Courey et al. (Journal of Molecular Biology, (1988), Vol. 202, pages 35-43).

Walker in view of Pardee et al. teach the processes of claims 121-136 as described above.

Walker in view of Pardee et al. do not teach one or more specific unmodified primers each of which primer comprises at least one non-complementary sequence to a distinct sequence of the specific nucleic acid such that upon hybridization to the specific nucleic acid at least one loop structure is formed.

Courey et al teaches one or more specific unmodified primers each of which primer comprises at least one non-complementary sequence to a distinct sequence of the specific nucleic acid such that upon hybridization to the specific nucleic acid at least one loop structure is formed (Figures 2, 5 and 6).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the loop forming supercoiling model of Courey et al. in the method of Walker in view of Pardee et al. , since Walker states, "The invention further relates to methods of generating amplified products which can function as probes or templates for sequence analysis (column 4, lines 41-47)." Courey et al provides further motivation as he states, "Lengths of cruciform arms are strongly dependent on sequence imperfections in the palindrome (page 36, column 1, lines 11-14)." An ordinary practitioner would have been motivated to combine the loop forming supercoiling model of Courey et al. in the method of Walker in view of Pardee et al. , in order to achieve the express advantages , as noted by Courey et al., of a method that provides the detection of sequence imperfections in a nucleic acid sample.

Allowable Subject Matter

12. Claims 150-167 are allowed in view of the absence of any prior art either teaching or suggesting an *in vivo* process for producing a specific nucleic acid, and all other elements of the claims.

Response to Amendment

13. In response to amendment, all previous 102(b) rejections for claims 142-149 have been withdrawn. However, new 112(first paragraph) and 112(second paragraph) rejections have been included and 102(e) as well as 103(a) rejections have been maintained properly.

Response to Arguments

14. Applicant's arguments with respect to claims 91-120 have been considered but are moot in view of the new ground(s) of (112(first paragraph) rejection. 102(e) rejection based on Walker reference has also been properly maintained because the rejection is based on the fact that the mere absence of a positive recitation, "independent of a requirement for the introduction of an endonuclease" in the amended claim 91 is not the basis for an exclusion. This limitation is interpreted as an optional choice in which endonuclease may or may not be present as desired by the experimenter. Moreover, in the presence of open "comprising" language, any material(s) or method step(s) can be included in the claim although it may not be a requirement.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that Pardee does not teach (I) one or more specific chemically-modified primers each of which primer is substantially complementary to a distinct sequence of the specific

nucleic acid, (ii) no contacting step between sample and RNA primers, and (iii) regeneration of primer binding site, thereby allowing a new priming event to occur. Applicant argues that the word "chemically modified primer", "regeneration of primer binding site," and"contacting step between sample and RNA primers" were not found in Pardee reference and only the word "enzymatically modified" are found. Applicant argues that because Pardee has a preferred embodiment of enzymatic modification of primers, Pardee is limited to the preferred embodiment. This argument is not persuasive. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Pardee has a preferred embodiment, this embodiment does not prevent the reference from suggesting broader embodiments in the disclosure and that this does not constitute a teaching away. Although Pardee reference uses enzymatically modified primers in some examples, Pardee clearly and expressly teaches the designing of chemically modified and customized primers by inserting inosine in the sequence (Column 14, lines 42-67). Moreover, Pardee teaches the contacting step between sample and RNA primers (Column 14, lines 15-20). Pardee also teaches the regeneration of primer-binding site, thereby allowing a new priming event to occur (Column 2, lines 8-19). Moreover, MPEP 2111 states, "Claims must be given their broadest reasonable interpretation. During patent

examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification". Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than it is justified. *In re Prater,* 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969)". In this case, any primers comprising of inosine, as taught by Pardee, can be considered as chemically modified.

In response to applicant's argument that Courey et al reference is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, influence of DNA sequence and supercoiling on the process of cruciform formation, as taught by Courey et al, is clearly relevant to the field of applicant's endeavor, and reasonably pertinent to the particular problem with which the applicant was concerned, i.e., an in vitro process for amplifying a nucleic acid.

Therefore, the 103(a) rejections have also been properly maintained.

Conclusion

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located In Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published In the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Chakrabarti

Patent Examiner

Art Unit 1634

February 14, 2003

JEFFREY FREDMAN
PRIMARY EXAMINER